Critical Care

An Evaluation of Intravenous Vitamin K for Warfarin Reversal: Are Guideline Recommendations Being Followed?

Ryan M. Rivosecchi, PharmD^{*}; Jeffrey Garavaglia, PharmD, BCPS[†]; and Sandra L. Kane-Gill, PharmD, MSc, FCCP, FCCM^{‡,¶}

ABSTRACT

Background: Vitamin K antagonists (eg, warfarin) remain the mainstay of anticoagulation therapy in the United States, with over 22 million prescriptions being filled annually. Unfortunately, warfarin therapy is difficult to manage and increases bleeding risk. The 2012 American College of Chest Physicians guidelines created a warfarin reversal algorithm that suggested the stringent use of intravenous vitamin K. **Objective:** The purpose of this evaluation was to determine the rates of adherence with guideline recommendations in clinical practice.

Method: A convenience sample of 3 months of intravenous vitamin K medication administration data (September to November 2013) was obtained to conduct a retrospective review. Patients with underlying hepatic dysfunction or lack of warfarin therapy were excluded. Vitamin K use was evaluated for consistency with the 2012 guidelines.

Results: A total of 364 patients were reviewed and 119 were included. Vitamin K utilization was consistent with guideline recommendations for a total of 30 (25.2%) patients. The most common site of active bleeding requiring reversal was head bleeds, consisting of 56.6% of bleeds. A single dose of 10 mg of vitamin K was the most frequently used dosing strategy. Fresh frozen plasma (73.3%) and four-factor prothrombin complex concentrate (36.7%) were the most commonly used factor products.

Conclusion: This evaluation demonstrates that there is a difference between clinical judgment and guideline adherence. True adherence with the guidelines may not be necessary; however, there is room for improvement in both the appropriateness and safety of intravenous vitamin K use.

Key Words—anticoagulation, anticoagulation reversal, guideline, phytonadione, vitamin K, warfarin

Despite the approval of multiple novel agents, vitamin K antagonists (VKAs) remain the mainstay of anticoagulation therapy. Warfarin controls the market in the United States with an estimated 22 million prescriptions being filled annually.¹ The volume of prescriptions is most likely driven by the familiarity with the long-standing product, comfort with the approach to reversal, and the wide array of US Food and Drug Administration (FDA)–approved indications, including cardiac valve replace-

ment, prevention and/or treatment of venous thromboembolism, and prevention and/or treatment of thromboembolic complications associated with atrial fibrillation. Vitamin K antagonists achieve their anticoagulant effects through the inhibition of vitamin K epoxide reductase (VKOR). For most indications, warfarin is dosed to achieve an international normalized ratio (INR) of 2.0 to 3.0.² When the INR drops below 2.0, patients are considered to be subtherapeutic and at a higher risk for thrombotic complications;

^{*}PGY-2 Critical Care Pharmacy Resident, University of Pittsburgh Medical Center (UPMC), Pittsburgh, Pennsylvania; [†]Assistant Professor, West Virginia University School of Pharmacy, Morgantown, West Virginia; [‡]Associate Professor, Department of Pharmacy, Critical Care Medicine, Biomedical Informatics and Clinical Translational Science Institute, University of Pittsburgh School of Pharmacy, Pittsburgh, Pennsylvania; [¶]Critical Care Medication Safety Pharmacist, UPMC, Pittsburgh, Pennsylvania. Corresponding author: Sandra L. Kane-Gill, PharmD, MS, FCCM, FCCP, University of Pittsburgh Medical Center, 3501 Terrace Street, Pittsburgh, PA 15213; e-mail: slk54@pitt.edu

conversely, when the INR rises above 3.0, patients are considered supratherapeutic and at a higher risk for bleeding events. Unfortunately, it has been shown in clinical practice to be exceedingly difficult to manage patients within this goal range, with average time in therapeutic range (TTR) typically reported between 50% to 70%.³ Increasing TTR is a challenge as VKA dosing requires highly individualized regimens due to genetic polymorphisms, extensive drug-drug and drug-food interactions, and alcohol intake, among others.⁴ Additionally, supratherapeutic INRs are not required to precipitate a bleeding event; in fact, over 60% of intracerebral hemorrhages occur when the INR is less than 3.0.⁵

Bleeding events while on warfarin are common, with an annual bleeding event rate between 1.7% and 3.4% in the United States.⁶ Hemorrhagic complications are responsible for more than 60,000 annual emergency department visits in VKA-treated patients.⁷ Of all VKA-treated patients, between 3% and 7% will require rapid reversal for either VKA-associated major bleed or for an emergent surgical procedure.⁸ The administration of vitamin K (phytonadione) has the ability to overcome the inhibition of VKOR and reverse anticoagulation. Although there are other therapies to correct excessive anticoagulation such as fresh frozen plasma (FFP) and prothrombin complex concentrates (PCC), vitamin K provides a longer lasting reversal.

Of the possible routes of administration, subcutaneous injection is generally not recommended due to erratic absorption and unpredictable results.⁹ Both oral and intravenous (IV) routes sufficiently reverse anticoagulation and result in similar reductions in INR at 24 hours, but the effects of IV administration are seen more rapidly.¹⁰ The use of IV vitamin K, however, is not without challenges and consequences. Intravenous administration requires the medication to be given over 30 minutes, which could prevent other IV medications from being administered. Although the rates of anaphylaxis after IV administration are low, approximately 3 cases per 10,000 administrations, it remains a risk that must be considered.¹¹ Finally if anticoagulation is reversed to below subtherapeutic levels unnecessarily, patients are at risk for thrombotic events until anticoagulation is resumed. The 2012 update of the American College of Chest Physicians (ACCP) guidelines for warfarin reversal provide a more reserved role of vitamin K reversal, stating it should only be administered with an INR greater than 10 with no evidence of bleed (oral therapy) or when a VKA-associated major bleed

is occurring (IV infusion with coagulation factors).² The purpose of this evaluation was to determine the rates of adherence with guideline recommendations in clinical practice.

METHOD

The Quality Improvement Board of the University of Pittsburgh Medical Center (UPMC) approved this project prior to commencement. It was performed at a large, urban, academic medical center that includes over 600 beds, including over 120 intensive care beds. A convenience sample of 3 months of medication administration data (September to November 2013) was obtained. A retrospective review of the electronic health record was then completed to extract the necessary data. Exclusion criteria included cirrhosis, acute hepatitis, and lack of warfarin therapy. Per guideline recommendations, adherence to the guidelines was defined as the use of 10 mg of IV vitamin K given in combination with either FFP or factor products for a major VKA-associated bleed. The guidelines, however, do not make any recommendations regarding often seen grey areas in clinical practice such as any VKA-associated bleeding event, emergent or life-threatening surgical procedures, or the use of IV vitamin K without concomitant FFP or factor product. Additionally, vitamin K doses less than 10 mg were considered a grey area of practice. For the purposes of this evaluation, inappropriate use was defined as not meeting either guideline recommendations or falling into a grey area of practice. Data collected included basic demographic information, admitting service, reason for admission, indication for anticoagulation, documented indication for reversal, baseline INR level, dosing strategy, and administration of other reversal agents, such as FFP and factor products.

RESULTS

A total of 364 patients were reviewed and 119 were included in the evaluation. The 2 main reasons for exclusion were lack of warfarin therapy (135 patients) and cirrhosis (70 patients). A full breakdown of excluded patients is located in **Figure 1**. The majority of patients were male and admitted by a surgical service to an intensive care unit. The primary reason for anticoagulation was atrial fibrillation (51.7%) followed by deep venous thrombosis (17.8%). Patient demographic information is located in **Table 1**. Overall, the administration of IV vitamin K was consistent with guideline recommendations in 30 patients (25.2%). Reversal

Figure 1. Breakdown of patient inclusion/exclusion. INR = international normalized ratio.

for intracerebral hemorrhage occurred in 36.7% of patients and reversal for any head bleed was the listed indication in 56.6% of all bleeds. A one-time IV order of 10 mg of vitamin K was the most regularly ordered reversal regimen (50%). FFP was the most frequent additional reversal product utilized in 22 patients, whereas four-factor PCC (4F-PCC) was used in 11. A combination of FFP and 4F-PCC was administered in 5 patients. Notably, no patient received three-factor PCC (3F-PCC) (Table 3). The median INR at time of reversal was 2.4 (1.7-3.0) with 70% of patients experiencing their bleeding episode with an INR less than 3.

While evaluating grey areas in clinical practice, an additional 35 patients were identified. Sixteen of these patients received therapy for reversal for urgent or emergent surgery, and 19 experienced a VKA-associated bleed. A full breakdown of patients considered to be in the grey areas of practice is given in Tables 2 and 3.

The primary reason for inappropriate use of vitamin K was elevated INR (35.7%) and for non-emergent surgical procedures (42.9%). The median baseline INR for patients considered inappropriate was within therapeutic range, at 2.8. Additionally, this

group was administered a follow-up dose a median of 13.5 hours after first administration, whereas the clinically appropriate use group received an additional dose a median of 21 hours later. Notably, 1 patient experienced an anaphylactic-like response.

DISCUSSION

The results of this evaluation demonstrate that vitamin K use at UPMC is inconsistent with the ACCP 2012 guidelines.² Similar evaluations have reported similar results; however, our evaluation provides insight into adherence with the most recent guidelines.^{12,13} Van Berkel et al examined the impact of a multifaceted education on improving prescribing practices of vitamin K for warfarin reversal. Their study demonstrated an increase in adherence from 25% to 55.8% after implementation of the education based on the 2008 guidelines.¹³ There are a few key differences between Van Berkel et al's evaluation and our evaluation; Van Berkel et al examined the use of both oral and IV formulations of vitamin K, whereas we chose to focus on reversal using the IV formulation. This decision was made due to the change in the 2012 guidelines that recommended that this therapy only be used in the setting of a major VKA-associated bleed in conjunction with either FFP or PCC. Additionally, the previous study was conducted at a large community teaching hospital, whereas our evaluation took place at a large, urban, tertiary care center. This difference in population is evident with over half of our patients being in the intensive care unit at the time of vitamin K administration. Roughly 25% of patients were reversed for a head bleed, with this therapy being driven by the large neurovascular intensive care unit at UPMC.

We identified 3 grey areas in clinical practice that could be encountered in the hospital setting that are not explicitly addressed by the guidelines. These grey areas consisted of reversal of warfarin prior to emergent or life-threatening surgery, use of concurrent FFP or PCC, and vitamin K dosing other than 10 mg. Of the 35 patients identified to be in a grey area of clinical practice, 54.3% received a dose of vitamin K prior to urgent or emergent surgical intervention. The guidelines state that IV vitamin K should only be used in addition to FFP or PCC; however, we chose to consider sole administration of IV vitamin K as a reasonable consideration in the setting of a bleed. There were 10 patients (28.6%) who did not receive co-administration with a factor product. When any dose of 1 to 10 mg of vitamin K was considered, 17 patients fell within a grey area. As guidelines serve as a framework to make medical decisions, it is

Table 1. Baseline characteristics

Characteristics	Total (N = 119)	Guideline adherent (n = 30)
Male	65 (54.6)	20 (66.7)
Age, years	72 [62-81]	73.5 [68-84.2]
Height, cm	170 [163-178]	170 [165-178]
Weight, kg	82 [71.8-93]	74 [64-83]
Caucasian	101 (84.9)	25 (83.3)
Intensive care	62 (54.5)	23 (76.7)
Surgical admitting service	67 (56.3)	17 (56.7)
Reason for admission		
SOB	8 (6.7)	0 (0)
ICH	9 (7.5)	8 (6.7)
SDH	10 (8.3)	6 (5.0)
CVA	4 (3.3)	3 (2.5)
Infectious	9 (7.5)	0 (0)
Fall	11 (9.2)	5 (4.2)
Pain	13 (10.8)	2 (1.7)
Indication for anticoagulation		
DVT	21 (17.8)	3 (10.0)
PE	11 (9.3)	1 (3.3)
AF	61 (51.7)	16 (53.3)
CVA	6 (5.1)	4 (13.3)
Valvular	6 (5.1)	4 (13.3)
Other	7 (5.9)	2 (6.7)

Note: Values given as n (%) or median [IQR]. AF = atrial fibrillation; CVA = cerebrovascular accident; DVT = deep venous thrombosis; ICH = intracerebral hemorrhage; PE = pulmonary embolism; SDH = subdural hematoma; SOB = shortness of breath.

exceedingly difficult to encompass all clinical scenarios. In these situations, or grey areas, clinicians must use their judgment and prior experiences to guide the safe and efficacious use of medications.

The strength of guideline recommendation regarding VKA reversal is level 2C, which represents a weak recommendation based on low or very low quality evidence.² When there is an inadequate level of evidence to provide firm recommendations, it becomes less important to be “adherent” to the national guidelines and more important to have institutional guidelines that address grey areas. We also believe that there are improvements in the ordering process that can be made to increase the safe and appropriate use of vitamin K, such as the creation of order sets or education targeted to practices areas with high levels of inappropriate use. Our results will allow a multidisciplinary group to identify common

pitfalls in the ordering process and aid in the potential resolution of the problem. The educational techniques utilized by Van Berkel et al resulted in a large reduction in inappropriate use and could be used to assist in the education of both pharmacists and physicians.¹³

We believe evaluations similar to ours should be completed at other institutions that want to gain insight into their use of IV vitamin K for VKA reversal. One of the strengths of this evaluation was the exclusion of patients with any type of hepatic dysfunction, as INR is difficult to interpret in this patient population and this population has complex coagulopathy.¹⁴ This patient population needs to be considered as functionally different when reviewing medication orders for appropriateness. Also, completing this review over almost 2 years after the guideline release has allowed time for practitioners to become

Table 2. Breakdown of the indication for reversal

	Total (N = 119)	Guideline adherent (n = 30)	Grey areas in clinical practice (n = 35)
Reason for reversal			
Active bleed	41 (34.5)	30 (100)	19 (54.3)
Surgery	38 (31.9)	0 (0)	16 (45.7)
Elevated INR	27 (22.7)	0 (0)	0 (0)
Other	13 (10.9)	0 (0)	0 (0)
Site of active bleed			
SAH	3 (2.5)	1 (3.3)	2 (5.7)
IVH	1 (0.8)	1 (3.3)	0 (0.0)
ICH	14 (11.8)	11 (36.7)	3 (8.6)
SDH	12 (10.1)	8 (13.3)	4 (11.4)
GIB	4 (3.4)	4 (13.3)	0 (0)
Level of INR elevation			
<3	2 (1.7)	N/A	N/A
3-7	21 (17.6)		
7-10	2 (1.7)		
>10	2 (1.7)		
Baseline INR	2.6 [1.6-3.4]	2.4 [1.7-3.0]	2.6 [2-3.2]
Follow-up INR ^a	1.6 [1.4-2.0]	1.5 [1.3-1.7]	1.6 [1.4-1.8]
Time to follow-up INR, hours	4.5 [2-11.5]	3 [2-7.3]	3 [1.5-9]
Follow-up INR ^a drawn with morning labs	48 (40.4)	6 (20.0)	12 (35.3)

Note: Values given as *n* (%) or median [IQR]. GIB = gastrointestinal bleed; ICH = intracerebral hemorrhage; INR = international normalized ratio; IVH = intraventricular hemorrhage; SAH = subarachnoid hemorrhage; SDH = subdural hematoma.

^aFollow-up INR is defined as the first obtained INR after the administration of the intravenous vitamin K.

accustomed to the new recommendations. The retrospective nature of this project was a major limitation, as the possibility exists that patients with a high clinical suspicion of bleed were administered vitamin K but this notion was not documented in the medical record. We did not collect information on the ill effects of inappropriate reversal such as thromboembolism, prolonged hospitalization, or difficulty in achieving goal INR post administration. This is an important next step to consider in further evaluations.

CONCLUSIONS

This evaluation demonstrated that there is a substantial difference in the ACCP 2012 guideline recommendations for IV vitamin K for VKA-associated major bleeding and real-world practice. Due to the complexity of the decision about

whether to reverse a patient's anticoagulation, we do not believe that it is reasonable to achieve 100% congruence. We do believe, however, that we will be able to decrease the amount of inappropriate use through the education techniques that have been shown to be beneficial in the literature. We are advocating for other institutions to complete an evaluation similar to ours to determine whether a problem exists, followed by the adoption of institution-specific policies that increase the appropriate use of IV vitamin K therapy.

ACKNOWLEDGMENTS

The authors of this manuscript have no disclosures to report.

At the time of this work, Dr. Garavaglia was a clinical pharmacist at UPMC, Pittsburgh, Pennsylvania.

Table 3. Breakdown of reversal strategies utilized

	Total (N = 119)	Guideline adherent (n = 30)	Grey areas in clinical practice (n = 35)
Vitamin K dose			
1 mg	9 (7.6)	0 (0)	0 (0)
2 mg	5 (4.2)	0 (0)	2 (5.7)
2.5 mg	1 (0.8)	0 (0)	0 (0)
5 mg	32 (26.9)	0 (0)	15 (42.9)
10 mg	72 (60.5)	30 (100)	47 (71.9)
Number of vitamin K doses			
1	89 (74.8)	15 (50)	31 (88.6)
2	5 (4.2)	6 (16.7)	0 (0)
3	12 (10.1)	9 (30)	2 (5.7)
4	5 (4.2)	0 (0)	2 (5.7)
5	1 (0.8)	1 (3.3)	0 (0)
Hours elapsed between multiple administrations	21 [8-25]	24 [14.5-27]	15 [7.5-21]
Other reversal strategies used			
Any	75 (63.2)	30 (100)	25 (71.4)
FFP	59 (49.6)	22 (73.3)	21 (60.0)
rFVIIa	2 (1.7)	2 (6.7)	0 (0)
4F-PCC	22 (18.5)	11 (36.7)	8 (22.9)
3F-PCC	0 (0)	0 (0)	0 (0)
Other	1 (0.8)	1 (3.3)	0 (0)

Note: Values given as n (%) or median [IQR]. FFP = fresh frozen plasma; rFVIIa = activated recombinant factor VII; 3F-PCC = three factor–prothrombin complex concentrate; 4F-PCC = four factor–prothrombin complex concentrate.

REFERENCES

1. IMS Institute for Healthcare Informatics. Data from the US National Prescription Audit; MAT (moving annual total); August 2011 - July 2012.
2. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th ed.). *Chest*. 2012;141(2 suppl):e152S-e184S.
3. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Risk-adjusted percent time in therapeutic range as a quality indicator for outpatient oral anticoagulation: Results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). *Circ Cardiovasc Qual Outcomes*. 2011;4(1):22-29.
4. Watson HG1, Baglin T, Laidlaw SL, Makris M, Preston FE. A comparison of the efficacy and rate of response to oral and intravenous Vitamin K in reversal of over-anticoagulation with warfarin. *Br J Haematol*. 2001;115(1):145-149.
5. Shehab N, Sperling LS, Kegler SR, Budnitz DS. National estimates of emergency department visits for hemorrhage-related adverse events from clopidogrel plus aspirin and from warfarin. *Arch Intern Med*. 2010;170(21):1926-1933.
6. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed.). *Chest*. 2008;133(suppl):160s-198s.
7. Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. *Arch Intern Med*. 2004;164(8):880-884.
8. Libby EN, Garcia DA. A survey of oral vitamin K use by anticoagulation clinics. *Arch Intern Med*. 2002;162:1893-1896.
9. Nee R, Doppenschmidt D, Donovan DJ, Andrews TC. Intravenous versus subcutaneous vitamin K1 in reversing excessive oral anticoagulation. *Am J Cardiol*. 1999;83(2):286-288.

10. Pirmohamed M. Warfarin: Almost 60 years old and still causing problems. *Br J Clin Pharmacol*. 2006;62(5):509-511.
11. Riegert-Johnson DL, Volcheck GW. The incidence of anaphylaxis following intravenous phytonadione (vitamin K1): A 5-year retrospective review. *Ann Allergy Asthma Immunol*. 2002;89(4):400-406.
12. Fan J, Armitstead JA, Adams AG, Davis GA. A retrospective evaluation of vitamin K1 therapy to reverse the anticoagulant effect of warfarin. *Pharmacotherapy*. 2003;23(10):1245-1250.
13. Van Berkel MA, Crannage AJ, Murphy JA. Evaluation of education on the appropriate use of vitamin K in warfarin reversal in adult inpatients. *Hosp Pharm*. 2013;48(8):662-667.
14. Koliscak L, Maynor L. Pharmacologic prophylaxis against venous thromboembolism in hospitalized patients with cirrhosis and associated coagulopathies. *Am J Health Syst Pharm*. 2012;69(8):658-663. ■